PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing: 02 June 2000 (02.06.00)	
International application No.: PCT/EP99/08778	Applicant's or agent's file reference: LEA33270-PC
International filing date: 15 November 1999 (15.11.99)	Priority date: 25 November 1998 (25.11.98)
Applicant: HIMMLER, Thomas et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International preliminary Examining Authority on:

27 March 2000 (27.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 338.83.38

Translation 16E1

1626

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 0050/049574	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP99/09004	International filing date (*day/month/year*) 23 November 1999 (23.11.99)	Priority date (*day/month/year*) 27 November 1998 (27.11.98)
International Patent Classification (IPC) or national classification and IPC C07D 235/30		
Applicant BASF AKTIENGESELLSCHAFT		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29 May 2000 (29.05.00)	15 December 2000 (15.12.2000)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP99/09004

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-33, as originally filed.
pages _____, filed with the demand,
pages _____, filed with the letter of _____.
pages _____, filed with the letter of _____.

☒ the claims, Nos. 1-20, as originally filed.
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____.
Nos. _____, filed with the letter of _____.

☐ the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____.
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-20	YES
	Claims		NO
Inventive step (IS)	Claims	1-20	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-20	YES
	Claims		NO

2. Citations and explanations

This report makes reference to the following documents:

D1: WO-A-97/04771 (NEWCASTLE UNIVERSITY VENTURES LIMITED), 13 February 1997 (1997-02-13), mentioned in the application

D2: WO-A-98/33802 (NEWCASTLE UNIVERSITY VENTURES LIMITED), 6 August 1998 (1998-08-06).

Novelty:

The subject matter of the present application meets the requirement of PCT Article 33(2) for the following reasons:

The benzimidazole derivatives of Formulae (Ia), (Ib) as per present Claim 1 are defined by the substituents R^1, R^4 and A; A, which is the substituent in position 2, stands for a heterocyclic ring.

D1 likewise discloses 2-aryl-substituted benzimidazole derivatives but the aryl definition given therein does not include heterocycles.

D2 discloses quinazolinone derivatives.

The present Claims 1-20 are therefore novel.

Inventive step:

The present application meets the requirements of PCT Article 33(3) for the following reasons (however, see the last sentence of this paragraph): The closest prior art is represented by D1. The compounds claimed in D1 are also useful as inhibitors of the PARP enzyme. As already mentioned above, the present compounds differ from those of D1 by the heteroaromatic substituents in position 2 of the benzimidazole unit. A person skilled in the art would not arrive at the structural features of the present compounds either by any obvious structural variation within D1 itself or by any combination with D2, which lays claim to compounds having equivalent pharmaceutical properties. Assuming that the exemplary compounds listed have been (positively) tested, an inventive step can be recognised in the present application.

Industrial applicability:

In the PCT Contracting States, there are no uniform criteria for assessing the industrial applicability of 5-20 in their present form. Patentability can also depend on the wording of the claims. The EPO, for example, does not recognise the industrial applicability of claims to the use of a compound in a medical treatment; it does, however, allow claims to the first use of a known compound in a medical treatment or to the use of such a compound in the manufacture of a drug for a new medical treatment.

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

The present application does not comply with PCT Rule 5 because it does not cite the relevant prior art (D2).

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The expression "prodrug" used in Claim 1, without any corresponding structural indications, does not meet the requirements of PCT Article 6 because a person skilled in the art cannot ascertain without unreasonable effort what structures fall under said prodrugs. Furthermore, the application does not contain adequate disclosure regarding metabolism, conditions, etc., and therefore said term also fails to comply with PCT Article 5.

Moreover, the description is not consistent with the claims (see page 10, explanation of diagrams 2 and 3) in that "benzoic acids such as IX", "benzonitriles such as XIII", "benzaldehyde V", etc. are disclosed, while variable A in the claims could never be benzole. In addition, "benzoic acid XI" is converted into "amide XII" in line 35. Both designations are inconsistent with the formula designations used in the drawing.

Unlike the claims, the description contains a $CO-R^7$ variable (see page 6, line 33).

The use as per Claim 9 of the present compound against Parkinson's disease does not appear to be supported by the description (see page 11).

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference LEA33270-PC	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP99/08778	International filing date (*day/month/year*) 15 November 1999 (15.11.99)	Priority date (*day/month/year*) 25 November 1998 (25.11.98)
International Patent Classification (IPC) or national classification and IPC C07D 471/04, A61K 31/4709, A61P 31/04, C07D 471/04, 221/00		
Applicant BAYER AKTIENGESELLSCHAFT		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27 March 2000 (27.03.00)	30 August 2000 (30.08.2000)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP99/08778

I. Basis of the report

1. This report has been drawn on the basis of (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

☐ the international application as originally filed.

☒ the description, pages 1-23, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. 1-11, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. _____, filed with the letter of _____,
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1/6-6/6, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

4. Additional observations, if necessary:

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1 - 11	YES
	Claims		NO
Inventive step (IS)	Claims	1 - 11	YES
	Claims		NO
Industrial applicability (IA)	Claims	1 - 11	YES
	Claims		NO

2. Citations and explanations

1 The present application relates to

(i) the semi-hydrochloride of 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo-[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid (CCDC semi-hydrochloride) (Claims 1 - 4),

(ii) methods for preparing it (Claims 5 - 8),

(iii) medicaments containing CCDC semi-hydrochloride (Claim 9) and

(iv) the use of CCDC semi-hydrochloride to produce a medicament (Claims 10 and 11).

2 This report makes reference to the following document:

D1: WO-A-97/31001 (BAYER AG) 28 August 1997; mentioned in the application.

3 Novelty

D1 describes 8-cyano-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo-[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acids, pharmaceutically useful acid addition salts thereof and the use

.../...

(Continuation of V.2)

thereof in antibacterial agents. CCDC and its hydrochloride are already described in D1 (page 15, Examples 1 and 2), whereas the CCDC semi-hydrochloride now claimed represents a novel selection from the acid addition salts generally claimed in D1.

4 Inventive step

The present application describes a particularly high water solubility of CCDC semi-hydrochloride (19 wt.%) compared with the known CCDC semi-hydrochloride (2.8 wt.%) and with the zwitterionic CCDC (0.02 wt.%).

With D1 as its point of departure, the present application is understood to address the problem of providing a salt of CCDC which is more soluble in water and therefore pharmaceutically more advantageous.

Since the available prior art contains no suggestion whatsoever of special solubility properties of particular salts, the problem to be solved by the present application appears to be solved in a non-obvious manner by the provision of CCDC semi-hydrochloride. The criterion of inventive step therefore appears to be satisfied by CCDC semi-hydrochloride (Claims 1 - 4) and hence for the subjects of Claims 5 - 11 as well.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The semi-hydrochlorides of Claims 1 and 2 appear to be one and the same object; it therefore seems appropriate to define Claim 2 as dependent on Claim 1. The expression "high and medium intensity" used in Claims 2 and 3 is vague and imprecise makes the definition of the above-mentioned claims unclear (PCT Article 6). It would therefore seem appropriate for the expression to which objection is raised to be clarified as on page 5, line 9.

Claims 4 - 8 are unclear, because the accessibility of CCDC semi-hydrochloride from the difluoro compound of formula (II) (Hal = F) by the method steps indicated in the claims seems doubtful. In addition, the use of "e.g." in Claims 4 and 5 makes the technical feature in item b of the claims unclear. For the sake of completeness, it should be noted that (II) and (III) are reacted "in the presence of a base" according to Claim 5 but only "optionally in the presence of a base" according to Claim 4.

VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS

PCT

INTERNATIONALER VORLÄUFIGER PRÜFUNGSBERICHT

(Artikel 36 und Regel 70 PCT)

Aktenzeichen des Anmelders oder Anwalts	WEITERES VORGEHEN	siehe Mitteilung über die Übersendung des internationalen vorläufigen Prüfungsbericht (Formblatt PCT/IPEA/416)
LEA33270-PC Th		
Internationales Aktenzeichen	Internationales Anmeldedatum *(Tag/Monat/Jahr)*	Prioritätsdatum *(Tag/Monat/Tag)*
PCT/EP99/08778	15/11/1999	25/11/1998
Internationale Patentklassification (IPK) oder nationale Klassifikation und IPK		
C07D471/04		
Anmelder		
BAYER AKTIENGESELLSCHAFT et al		

1. Dieser internationale vorläufige Prüfungsbericht wurde von der mit der internationale vorläufigen Prüfung beauftragte Behörde erstellt und wird dem Anmelder gemäß Artikel 36 übermittelt.

2. Dieser BERICHT umfaßt insgesamt 5 Blätter einschließlich dieses Deckblatts.

   ☐ Außerdem liegen dem Bericht ANLAGEN bei; dabei handelt es sich um Blätter mit Beschreibungen, Ansprüchen und/oder Zeichnungen, die geändert wurden und diesem Bericht zugrunde liegen, und/oder Blätter mit vor dieser Behörde vorgenommenen Berichtigungen (siehe Regel 70.16 und Abschnitt 607 der Verwaltungsrichtlinien zum PCT).

   Diese Anlagen umfassen insgesamt Blätter.

3. Dieser Bericht enthält Angaben zu folgenden Punkten:

   - I ☒ Grundlage des Berichts
   - II ☐ Priorität
   - III ☐ Keine Erstellung eines Gutachtens über Neuheit, erfinderische Tätigkeit und gewerbliche Anwendbarkeit
   - IV ☐ Mangelnde Einheitlichkeit der Erfindung
   - V ☒ Begründete Feststellung nach Artikel 35(2) hinsichtlich der Neuheit, der erfinderische Tätigkeit und der gewerbliche Anwendbarkeit; Unterlagen und Erklärungen zur Stützung dieser Feststellung
   - VI ☐ Bestimmte angeführte Unterlagen
   - VII ☐ Bestimmte Mängel der internationalen Anmeldung
   - VIII ☒ Bestimmte Bemerkungen zur internationalen Anmeldung

Datum der Einreichung des Antrags	Datum der Fertigstellung dieses Berichts
27/03/2000	30.08.2000
Name und Postanschrift der mit der internationalen vorläufigen Prüfung beauftragten Behörde:	Bevollmächtigter Bediensteter
Europäisches Patentamt D-80298 München Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Weisbrod, T Tel. Nr. +49 89 2399 8931

Formblatt PCT/IPEA/409 (Deckblatt) (Januar 1994)

INTERNATIONALER VORLÄUFIGER PRÜFUNGSBERICHT

Internationales Aktenzeichen PCT/EP99/08778

I. Grundlage des Berichts

1. Dieser Bericht wurde erstellt auf der Grundlage (*Ersatzblätter, die dem Anmeldeamt auf eine Aufforderung nach Artikel 14 hin vorgelegt wurden, gelten im Rahmen dieses Berichts als "ursprünglich eingereicht" und sind ihm nicht beigefügt, weil sie keine Änderungen enthalten.*):

Beschreibung, Seiten:

1-23 ursprüngliche Fassung

Patentansprüche, Nr.:

1-11 ursprüngliche Fassung

Zeichnungen, Blätter:

1/6-6/6 ursprüngliche Fassung

2. Aufgrund der Änderungen sind folgende Unterlagen fortgefallen:

☐ Beschreibung, Seiten:
☐ Ansprüche, Nr.:
☐ Zeichnungen, Blatt:

3. ☐ Dieser Bericht ist ohne Berücksichtigung (von einigen) der Änderungen erstellt worden, da diese aus den angegebenen Gründen nach Auffassung der Behörde über den Offenbarungsgehalt in der ursprünglich eingereichten Fassung hinausgehen (Regel 70.2(c)):

4. Etwaige zusätzliche Bemerkungen:

V. Begründete Feststellung nach Artikel 35(2) hinsichtlich der Neuheit, der erfinderischen Tätigkeit und der gewerblichen Anwendbarkeit; Unterlagen und Erklärungen zur Stützung dieser Feststellung

1. Feststellung

Neuheit (N)	Ja:	Ansprüche	1-11
	Nein:	Ansprüche	
Erfinderische Tätigkeit (ET)	Ja:	Ansprüche	1-11
	Nein:	Ansprüche	
Gewerbliche Anwendbarkeit (GA)	Ja:	Ansprüche	1-11
	Nein:	Ansprüche	

2. Unterlagen und Erklärungen

sieh Beiblatt

VIII. Bestimmte Bemerkungen zur internationalen Anmeldung

Zur Klarheit der Patentansprüche, der Beschreibung und der Zeichnungen oder zu der Frage, ob die Ansprüche in vollem Umfang durch die Beschreibung gestützt werden, ist folgendes zu bemerken:

si he Beiblatt

Zu Punkt V

Begründete Feststellung nach Artikel 35(2) hinsichtlich der Neuheit, der erfinderischen Tätigkeit und der gewerblichen Anwendbarkeit; Unterlagen und Erklärungen zur Stützung dieser Feststellung

1 Die vorliegende Anmeldung bezieht sich auf
(i) das Semihydrochlorid von 8-Cyan-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo-[4.3.0]nonan-8-yl)-6-fluor-1,4-dihydro-4-oxo-3-chinolincarbonsäure (CCDC-Semihydrochlorid) (Ansprüche 1-4),
(ii) Verfahren zu seiner Herstellung (Ansprüche 5-8),
(iii) Arzneimittel, die CCDC-Semihydrochlorid enthalten (Anspruch 9) und
(iv) die Verwendung von CCDC-Semihydrochlorid zur Herstellung eines Arzneimittels (Ansprüche 10 und 11).

2 In diesem Bescheid wird folgendes Dokument genannt.

D1: WO 97 31001 A (BAYER AG) 28. August 1997; in der Anmeldung erwähnt.

3 Neuheit

D1 beschreibt 8-Cyan-1-cyclopropyl-7-(1S,6S-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluor-1,4-dihydro-4-oxo-3-chinolincarbonsäuren, pharmazeutisch verwendbare Säureadditionssalze davon und ihre Verwendung in antibakteriellen Mitteln. CCDC und ihr Hydrochlorid werden bereits in D1 beschrieben (Seite 15, Beispiele 1 und 2), während das jetzt beanspruchte CCDC-Semihydrochlorid eine neue Auswahl der in D1 allgemein beanspruchten Säureadditionssalzen darstellt.

4 Erfinderische Tätigkeit

Die vorliegende Anmeldung beschreibt eine besonders hohe Wasserlöslichkeit für CCDC-Semihydrochlorid (19% w/w) im Vergleich zum bekannten CCDC-Hydrochlorid (2.8% w/w) und zum zwitterionischem CCDC (0.02% w/w).
Ausgehend von D1 als nächstem Stand der Technik, kann die zu lösende Aufgabe der Anmeldung in der Bereitstellung eines besser wasserlöslichen und damit pharmazeutisch vorteilhafteren Salzes von CCDC gesehen werden.

Da der zur Verfügung stehende Stand der Technik keinerlei Hinweis auf besondere Löslichkeitseigenschaften bestimmter Salze enthält, erscheint die Aufgabe der vorliegenden Anmeldung mit der Bereitstellung von CCDC-Semihydrochlorid auf nicht naheliegende Weise gelöst. Das Kriterium der erfinderischen Tätigkeit scheint demnach für CCDC-Semihydrochlorid (Ansprüche 1-4) und infolgedessen auch für den jeweiligen Gegenstand der Ansprüche 5-11 erfüllt zu sein.

Zu Punkt VIII
Bestimmte Bemerkungen zur internationalen Anmeldung

Beim Semihydrochlorid der Ansprüche 1 und 2 scheint es sich wohl um denselben Gegenstand zu handeln; aus diesem Grund erscheint es zweckmässig Anspruch 2 als abhängig von Anspruch 1 zu definieren. Die in dem Ansprüchen 2 und 3 benutzte Formulierung "hoher und mittlerer Intensität" ist verschwommen und unpräzise und führt dazu, daß die Definition der genannten Ansprüche unklar ist (Artikel 6 PCT). Es würde deshalb zweckmäßig erscheinen die beanstandete Formulierung gemäß Seite 5, Zeile 9, zu präzisieren.
Die Ansprüche 4-8 sind unklar, da die Zugänglichkeit von CCDC-Semihydrochlorid aus der Difluor-Verbindung der Formel (II) (Hal = F) über die in den Ansprüchen angegeben Verfahrensschritte fragwürdig erscheint. Zudem führt die Verwendung des "z.B." in den Ansprüchen 4 und 5 dazu, daß das technische Merkmal unter Punkt b der Ansprüche unklar ist. Vollständigheitshalber sei darauf hingewiesen, daß (II) und (III) gemäß Anspruch 5 "in Gegenwart einer Base" gemäß Anspruch 4 aber lediglich "gegebenfalls in Gegenwart einer Base" umgesetzt werden.